

December 9 and 10, 2003 FIFRA SAP MEETING AGENDA

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

December 9 and 10, 2003

FIFRA SAP WEB SITE <http://www.epa.gov/scipoly/sap/>

OPP Docket Telephone: (703)305-5805

**Proposed Science Policy: PPAR- α Agonist-Mediated
Hepatocarcinogenesis in Rodents and Relevance
to Human Health Risk Assessments**

TUESDAY, DECEMBER 9, 2003

HOLIDAY INN NATIONAL AIRPORT

2650 JEFFERSON DAVIS HIGHWAY

ARLINGTON, VIRGINIA 22202

703-684-7200

Please note that all times are approximate.

- **8:30 AM Meeting Opening** - Stephen M. Roberts, Ph.D. (Chair of the FIFRA SAP)
- **8:35 AM Introduction of Panel Members** - Gary E. Isom, Ph.D. (FIFRA SAP Session Chair)
- **8:40 AM Administrative Procedures by Designated Federal Official** - Mr. Steven Knott
- **8:45 AM Welcome** - Mr. Joseph Merenda, Jr. (Director, Office of Science Coordination and Policy, Office of Prevention, Pesticides and Toxic Substances, EPA)
- **8:50 AM Opening Remarks** - Mr. William Jordan (Office of Pesticide Programs, Office of Prevention, Pesticides, and Toxic Substances, EPA)
- **9:00 AM Introduction and Background** - Margaret Stasikowski, M.P.H. (Health Effects Division, Office of Pesticide Programs, EPA)
- **9:10 AM Presentation on PPAR α Agonist-Induced Rodent Tumors: Modes of Action and Human Relevance** - Jeff Peters, Ph.D. (Penn State University)
- **9:50 AM Break**
- **10:05 AM Proposed Science Policy: PPAR- α Agonist-Mediated Hepatocarcinogenesis in Rodents and Relevance to Human Health Risk Assessments** - Elizabeth Mendez, Ph.D. (Health Effects Division, Office of Pesticide Programs, EPA)
- **10:45 AM Public Comments**
- **12:00 PM Lunch**
- **1:00 PM Public Comments Continued**

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• 2:00 PM Questions to the Panel

OVERVIEW:

Developments in the area of research on peroxisome proliferating chemicals have led to a reevaluation of the state of the science to characterize the mode(s) of action (i.e., PPAR α agonism) and the human relevance of rodent tumors induced by PPAR α agonists. Recently, the ILSI Risk Science Institute (ILSI RSI) convened a large expert technical group (ILSI document, 2003) to evaluate new information on the association between PPAR α agonism and the induction of tumors by peroxisome proliferating chemicals. OPPTS considered the 2003 ILSI report as well as the pertinent scientific literature in developing its proposed science policy. Please provide comments and advice on the following questions. In addressing these, questions consider the completeness of the data sets evaluated.

Question 1 - Rodent PPAR α Mode of Action for Hepatocarcinogenesis

OPPTS has concluded that there is sufficient weight of evidence to establish the mode of action for PPAR α agonist-induced rodent hepatocarcinogenesis. It is proposed in the OPPTS document that PPAR α agonists activate PPAR α leading to an increase in cell proliferation and a decrease in apoptosis, and eventually further clonal expansion of preneoplastic cells and formation of liver tumors. The key events in PPAR α agonist-induced hepatocarcinogenesis may be classified as either causal (required for this MOA) or associative (marker of PPAR α agonism).

Please comment on the weight of evidence and key events for the proposed mode of action for the PPAR α agonist-induced rodent hepatocarcinogenesis. Please comment on the adequacy of the data available to identify the key events in the PPAR α MOA. Discuss whether the uncertainties and limitations of these data have been adequately characterized.

• 3:00 PM Break

• 3:15 PM Question to the Panel Continued

Question 2 - Relative Sensitivity of Fetal, Neonatal, and Adult Rodent

OPPTS has provided a review of the ontogeny of PPAR α expression and peroxisomal assemblage during fetal and postnatal development in rodents as well as an analysis of the available data evaluating effects on peroxisomal proliferation, peroxisomal enzyme activity, and liver weights following exposure to PPAR α agonists during fetal and postnatal development in rats and mice (see Section V of the OPPTS Document). Based on this analysis, OPPTS concluded that fetal and neonatal rats do not exhibit an increased sensitivity to PPAR α agonist-induced hepatocarcinogenicity relative to the adult rodent. Therefore, any conclusions regarding this mode of action in adult rodents would also apply to young rodents, and similarly any conclusions regarding the relevance of this mode of action for human hepatocarcinogenesis would apply to the young, as well as the adults.

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Please comment on the weight of the evidence approach and mechanistic data used to support this conclusion.

- **5:30 PM** **Adjournment**

**WEDNESDAY, DECEMBER 10, 2003
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ARLINGTON, VIRGINIA 22202
703-684-7200**

Please note that all times are approximate.

- **8:30 AM** **Meeting Opening** - Stephen M. Roberts, Ph.D. (Chair of the FIFRA SAP)
- **8:35 AM** **Introduction of Panel Members** - Gary E. Isom, Ph.D. (FIFRA SAP Session Chair)
- **8:40 AM** **Administrative Procedures by Designated Federal Official** - Mr. Steven Knott
- **8:45 AM** **Follow-up from Previous Day's Discussion** - Margaret Stasikowski, M.P.H. and Elizabeth Mendez, Ph.D. (Health Effects Division, Office of Pesticide Programs, EPA)
- **9:00 AM** **Questions to the Panel Continued**

Question 3 - Human Relevance

OPPTS has provided an analysis of a variety of in vitro and in vivo studies on the key events pertaining to PPAR α agonist-induced hepatocarcinogenesis with hamsters, guinea pigs, non-human primates, and humans. Based on the weight of the evidence, OPPTS concludes that although PPAR α agonists can induce liver tumors in rodents and while PPAR α is functional in humans, quantitatively, humans and nonhuman primates are refractory to the hepatic effects of PPAR α agonists.

Therefore, OPPTS is proposing the following scientific policy:

When liver tumors are observed in long term studies in rats and mice, and 1) the data are sufficient to establish that the liver tumors are a result of a PPAR α agonist MOA and 2) other potential MOAs have been evaluated and found not operative, the evidence of liver tumor formation in rodents should not be used to characterize potential human hazard.

Please comment on the data and weight of evidence regarding the hepatic effects of

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PPAR α agonists in humans, and please comment on the proposed OPPTS's science policy regarding human relevance.

• **10:30 AM Break**

• **10:45 AM Question to the Panel Continued**

Question 4 - Data Requirements

OPPTS has proposed a data set that would be sufficient to demonstrate that PPAR α agonism is the mode of action for the induction of rodent liver tumors. The data set includes evidence of PPAR α agonism (i.e. from an in vitro reporter gene assay), in vivo evidence of an increase in number and size of peroxisomes, increases in the activity of acyl CoA oxidase, and hepatic cell proliferation. The in vivo evidence should be collected from studies designed to provide the data needed to show dose-response and temporal concordance between precursor events and liver tumor formation.

Please comment in general on the proposed data set and particularly on its adequacy to demonstrate that a PPAR α agonist-mediated MOA is operating in rodent hepatocarcinogenesis.

• **12:00 PM Lunch**

• **1:00 PM Questions to the Panel Continued**

Question 5 - Other Tumors Induced by PPAR α Agonists

Some PPAR α agonists may also induce pancreatic acinar cell and Leydig cell tumors in rats and modes of action involving agonism of PPAR α have been proposed. An in depth analysis of these tumors is provided in the 2003 ILSI technical panel report. Based on this analysis, OPPTS agrees that the data available to date are insufficient to support the proposed MOAs.

Thus, OPPTS is proposing the following science policy:

Given the limited evidence available to support that a chemical may induce pancreatic and Leydig cell tumors through a PPAR α agonist mode of action, the evidence is inadequate at this time to support a linkage between PPAR α agonism and formation of these tumor types. Thus, it is presumed that chemicals that induce pancreatic or Leydig cell tumors may pose a carcinogenic hazard for humans.

Please comment on OPPTS's conclusion that there is limited evidence that a chemical may induce pancreatic and Leydig cell tumors through a PPAR α agonist mode of action, and OPPTS's proposed science policy regarding other tumors induced by PPAR α agonists.

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• 3:00 PM Adjournment

As noted above, please be advised that agenda times are approximate. For further information, please contact the Designated Federal Official for this meeting, Mr. Steven Knott, via telephone: (202) 564-8450; fax: (202) 564-8382; or email: knott.steven@epa.gov.